REMARKS

A. Regarding the Amendments

Claims 1, 18, 31 and 63 have been amended, as set forth in the attached "Version With Markings To Show Changes Made." As amended, the claims are supported by the specification and the original claims. By these amendments, it has been made clear that the methods of the invention contain a step wherein the cell or population of cells in the method are lysed. Support for this addition can be found at, for example, page 20, lines 4-6 or in the Examples section of the application, on page 26-26, under the heading"Assay for Luciferase Activity." New claims 71-73 are supported by the specification, for example at page 20, lines 4-6. Additionally, claims 48-62, 69 and 70 have been cancelled as claims to the non-elected invention. Thus, upon entry of this Preliminary Amendment, claims 1-47 and 63-73 will be pending.

It is acknowledged that Applicant's response after the Final Office Action, mailed April 29, 2002 has been entered. The Examiner's attention is respectfully drawn to the fact that Applicant has presented herein several new arguments. Accordingly, detailed consideration by the Examiner of all arguments contained herein is respectfully requested.

B. Rejections Under 35 U.S.C. §112, first paragraph

Claims 1 to 47 and 63 to 68 are rejected in Paper No. 14 as allegedly not enabled under 35 U.S.C. §112, first paragraph. The rejection is respectfully traversed.

The Examiner has rejected the claims as allegedly not enabled, as the claims encompass a method in which whole, live cells in isolation of a subject's body are exposed to coelenterazine. In particular, the Examiner has alleged that "the specification fails to exemplify the claimed method for measuring the proliferation of intact cells in the presence or absence of a therapeutic agent..." Applicant respectfully disagrees. It is maintained, as previously set forth by Applicant, that the claimed method is an *in vitro* method that serves diagnostic, not therapeutic, purposes

and is not used in humans. It is respectfully submitted that one of skill in the art would be able to practice the claimed invention, including use of whole, live cells, as disclosed.

However, in the interest of advancing the prosecution of the claimed invention, Applicant has amended the independent claims of the invention to include the requirement that the cells of the method be lysed. As amended, the claims are fully enabled by the Example in the specification entitled "Assay for Luciferase Activity." As the methods of the invention are set forth in the examples, it is respectfully submitted that the claimed invention is enabled and that one of skill in the art would have been able to practice the methods of the invention without undue experimentation at the time of filing of the invention.

Accordingly, Applicant respectfully traverses the rejection of claims 1-47 and 63-68 as allegedly non enabled under 35 U.S.C. §112, first paragraph. As such, one of skill in the art would be able to practice the present invention, as set forth above, Therefore, claims 1-47 and 63-68 meet the enablement requirement of 35 U.S.C. §112, first paragraph. Accordingly, the removal of the rejection is requested.

C. Rejections Under 35 U.S.C. §112, second paragraph

Claims 1 to 47 and 63 to 68 are rejected as allegedly incomplete under 35 U.S.C. §112, second paragraph, for omitting essential steps. The rejection is respectfully traversed.

Applicant respectfully submits that the claims do not omit essential steps. As set forth by the Examiner in Paper No. 7, the steps allegedly omitted are: 1) a cellular lysate is prepared; 2) coelenterazine is added to the lysate; and 3) light emission data is collected from cells in the presence and absence of an agent. Applicant respectfully submits that these steps are not required for the practice of the present invention.

Applicant maintains that the above steps are not necessary steps. Initially, a step requiring that a cellular lysate be prepared is not necessary. Where lysing is used in the invention, it is a part of measuring the light emission data. As clarified to the Examiner in the telephonic conference on July 23, 2002, it is Applicant's position that lysing the cells is not necessary to measuring light emission data. In support of this position, Applicant respectfully directs the Examiner's attention to the language at page 20, lines 3-4, which states that the amount of coelentrazine will depend on the assay conditions, "e.g. whole cell, lysate, purified protein."

Applicant has previously asserted that coelenterazine is hydrophobic and it may therefore penetrate the cells without the assistance of a detergent to make the cell membrane permeable. Additional methods of screening cells are available to one of skill in the art besides lysing the cells. These other methods might include the use of the tetrazoleum component MTT or use of Trypan Blue. Both would allow assays of cellular proliferation without lysing the cells. Because other methods of screening cells are available and are known to those of skill in the art, Applicant respectfully submits that no steps have been omitted from claims 1-17, 18-30, 31-47 or 63-68.

However, in the interest of advancing the prosecution of the present application, the claims have been amended to include a lysing step in the independent claims. It is therefore requested that the rejection of claims 1-17, 18-30, 31-47 and 63-68 be removed.

Additionally, it is Applicant's position that a step requiring that coelenterazine (or other luciferase substrate) be added to the lysate is not necessary. As set forth above, when the cells are lysed, the coelenterazine may be added either as the cells are being lysed or after the cells are lysed. (Specification, page 20, lines 4-6.) Therefore it is not only unnecessary, but incorrect to add a step to the claims that requires that coelenterazine must be added to the lysate.

Finally, it was alleged in Paper No. 9 that claims 63-68 were missing a step to "light emission data is collected from cells in the presence and absence of an agent." Applicant

respectfully draws the Examiner's attention to claim 63 of the application, as filed, which contains language "measuring light emissions from the cells in the presence and absence of the agent..." It is unclear why these claims have been rejected as omitting this step. Applicant submits that the claim language contains a comparison of the emissions in the presence and absence of the agent and clarification or removal of this rejection is respectfully requested.

As the allegedly missing steps of the claimed invention are either unnecessary or included, as set forth above, it is respectfully requested that the rejection of claims 1-47 and 63-68 under 35 U.S.C. §112, second paragraph as allegedly omitting essential steps be withdrawn.

Claims 1-47 and 63-68 are rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to point out and distinctly claim the subject matter which applicant regards as the invention. Applicant respectfully traverses the rejection. Applicant respectfully submits that the following discussion was previously set forth in response to the Examiner's arguments presented in Paper No. 9. However, as the discussion was dismissed as appearing to not set forth any new grounds of traversal, it does not appear that the following was considered in drafting Paper No. 14. It is respectfully submitted that the following discussion does contain new grounds of traversal. Review and consideration of the discussion is therefore respectfully requested.

The Examiner's rejection of these claims is in regard to the terms "an agent" in line 3 of claim 1, "a cell" in line 3 of claim 18, "an agent" in line 5 of claim 31 and "cells" in line 3 of claim 63. Applicant respectfully submits that the use of these terms in the preamble of each respective claim is not limiting. Applicant respectfully stands by the statements Applicant made in Paper No. 9. The rejection of claims 1-17 alleges that the phrase "an agent" in line 3 of claim 1 is indefinite. This allegation is based on the fact that the term "an agent" is used in line 1 of the claim and therefore it is allegedly indefinite whether use of the term in line 3 refers to the same agent as in line 1. The use of the term "an agent" in line 1 is part of the preamble of the claim. Generally, a preamble is not considered limiting to a claim unless it breathes life and meaning

into the claim. (See MPEP 2111.02.) In the present invention, the claim following the transitional phrase "comprising" stands alone. It is therefore unnecessary for the term "an agent" in line 1 to serve as an antecedent basis for the use of "an agent" in line 3, or for the term "agent" in line 3 to be preceded by a definite article. As such, use of the indefinite article "an" is proper in line 3. This argument applies equally to the rejections of claims 18, 31 and 63.

In Paper No. 9, the Examiner's has stated that the preambles of claims 1, 18, 31 and 63 do breathe life and meaning into those claims, as required under MPEP 2111.02. The Examiner then poses the question:

> "In view of [MPEP 2111.02]...the Examiner wonders if applicant would still argue that the body of each claim in the instant application 'stands alone.' For example, would a claim to a method for determining the effect of an agent be a method for determining the effect of the agent, when the method does not comprise a step of 'determining the effect of the agent.'" (Quotations in Paper No. 9.)

In response to the Examiner's question, Applicant maintains that with regard to the terms "an agent" in line 3 of claim 1, "a cell" in line 3 of claim 18, "an agent" in line 5 of claim 31 and "cells" in line 3 of claim 63, the claims do stand alone.

As cited by the Examiner, MPEP 2111.02 in part states that "[i]f the body of a claim fully and intrinsically sets forth all of the limitations of the claimed invention, and the preamble merely states, for example, the purpose or intended use of the invention, rather than any distinct definition of any of the claimed invention's limitations, then the preamble is not considered a limitation and is of no significance to claim construction." With regard to the terms an agent" in line 1 of claim 1, "a cell" in line 1 of claim 18, "an agent" in line 1 of claim 31 and "cells" in line 2 of claim 63, these terms are part of the intended use of the invention. The claimed invention is "A method for determining the effect of an agent on cell proliferation..." (claim 1, emphasis added). The word "for" is defined by Merriam-Webster's Collegiate Dictionary as "a function

word to indicate purpose." (See www.webster.com.) Accordingly, the language of the prepositional phrase beginning with the word "for" in the preamble of claims 1, 18 and 31 indicates the purpose of the claim, and is therefore not considered a limitation and "and is of no significance to claim construction." (MPEP 2111.02.) As the phrase is of no significance in claim construction, the occurrence of the phrases "an agent" in line 3 of claim 1, "a cell" in line 3 of claim 18, "an agent" in line 5 of claim 31 are the first occurrences of those terms and should therefore be preceded with an indefinite article. Similarly, the preposition "to" is defined by Merriam-Webster's Collegiate Dictionary as "a function word to indicate purpose, intention, tendency, result, or end." (See www.webster.com.) Accordingly, the language of the prepositional phrase beginning with the word "to" in the preamble of claim 63 indicates the purpose of the claim, and is therefore not considered a limitation and "and is of nc significance to claim construction."

As the use of indefinite terms "an agent" in line 3 of claim 1, "a cell" in line 3 of claim 18, "an agent" in line 5 of claim 31 and "cells" in line 3 of claim 63 do not require an antecedent basis, as used, it is submitted that those claims are not indefinite under 35 U.S.C. §112. Accordingly, the removal of the rejection of claims 1-47 and 63-68 is respectfully requested.

D. Rejections Under 35 U.S.C. §103

Claims 1 to 47 and 63 to 68 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Cree in view of Virta, et al, Edinger, et al, Prosser, et al, and further in view of U.S. Pat. Nos. 5,292,658 A and 6,171,809 B1. The rejection is respectfully traversed.

35 U.S.C. § 103 requires that:

> "A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a

> whole would have been obvious to a person having ordinary skill in the art to which said subject matter pertains."

Additionally, for an invention to be obvious in light of a combination of references under 35 U.S.C. §103, 1) there must be a suggestion of motivation to combine the references, 2) there must be a reasonable expectation of success, and 3) the prior art references must teach or suggest all of the claim limitations. (See MPEP 2142). It is respectfully submitted that Cree in view of Virta, et al, Edinger, et al, Prosser, et al, and further in view of U.S. Pat. Nos. 5,292,658 A and 6,171,809 B1 does not meet these requirements, and therefore the claims are not obvious in light of these references.

Applicant's prior argument set forth how the combination of references lacked requirement 3 above, the references do not teach or suggest all of the claim limitations. Specifically, it was argued by Applicant that none of the references cited as allegedly rendering the present invention obvious teach or suggest that the effect of an agent on cell proliferation may be tested via measurement of light emission using *Renilla* luciferase. There is no suggestion or motivation to combine the references to achieve the claimed invention. The Examiner queries as to why the references were discussed individually when a 103 rejection is based on a combination of references. Specifically, the Cree reference was discussed first, as it was cited by the Examiner as the primary reference. Cree was shown to be lacking various features of the claimed invention. Then each of the secondary references was discussed individually to show how each reference did not teach the element lacking in the primary reference. The conclusion was therefore reached that in combination, the cited references did not teach all of the elements of the claimed invention. Therefore it was asserted that the rejection of claims 1-47 and 63-68 could not stand.

Specifically, Cree teaches determination of cell viability based on luminescence and an ATP based system. Therefore, in Cree, cell proliferation or viability is determined by the amount

of endogenous ATP using a firefly luciferase assay. In the present invention, however, transient transfected *Renilla* luciferase itself is used as a reporter to measure cell proliferation.

It is respectfully submitted that none of the other references cited by the Examiner teach or suggest an assay using transient transfected *Renilla* luciferase as a reporter to measure cell proliferation. Accordingly, the combination of references does not teach or suggest all of the claim elements of the claimed invention.

The remaining references are Virta, Edinger, Prosser and U.S. Pat. Nos. 5,292,658 A and 6,171,809 B1. These references are discussed individually below to show that none of the cited references, either alone or when combined with Cree or one another, teach or suggest the use of luminescence using transient transfected *Renilla* luciferase as a reporter to measure cell proliferation. The Virta reference discusses the connection between prokaryotic cell viability and light emission, but uses a known agent to establish this connection. Virta contains no teaching or suggestion to use the process in reverse, using the light emission of *Renilla* luciferase to determine the effect of an agent of unknown properties on proliferation.

The Edinger reference also does not teach or suggest the use of *Renilla* luciferase to determine the effect of an agent on cellular proliferation, or transient transfected *Renilla* luciferase as a reporter to measure cell proliferation. Accordingly, this reference does not teach or suggest the present invention.

The teachings of the Prosser reference and U.S. Pat. Nos. 5,292,658 A and 6,171,809 B1 cannot overcome the deficiencies of the Cree, Virta and Edinger references. None of the cited references in any combination teach or suggest the use of transient transfected *Renilla* luciferase as a reporter to measure cell proliferation.

Cree, et al., Virta, et al, Edinger, et al, Prosser, et al, and U.S. Pat. Nos. 5,292,658 A and 6,171,809 B1 are provided as discussed above. None of the cited references, in any

combination, teach or suggest all of the claimed aspects to the present invention. Accordingly, it is respectfully requested that this rejection of the claims under 35 U.S.C. § 103, be removed.

CONCLUSION

In summary, for the reasons set forth herein, Applicants maintain that claims 1-47 and 63-80 clearly and patentably define the invention, respectfully request that the Examiner reconsider the various grounds set forth in the Office Action, and respectfully request the allowance of the claims which are now pending.

If the Examiner would like to discuss any of the issues raised in the Office Action, Applicant's representative can be reached at (858) 677-1456. No fee is deemed necessary in connection with the filing of this response. However, if any fee is deemed necessary, the Commissioner is authorized to charge (or apply any credits to) Deposit Account 50-1355.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS

1. (Twice amended) An *in vitro* method for determining the effect of an agent on cell proliferation using cells containing a *Renilla* luciferase polypeptide or a polynucleotide encoding a *Renilla* luciferase, comprising:

[contacting a cell containing a *Renilla* luciferase polypeptide or a polynucleotide encoding a *Renilla* luciferase with an agent suspected of modulating cell proliferation under conditions that allow the agent and the cell to interact; and]

lysing the cells that have been contacted with an agent suspected of modulating cell proliferation to form a lysate; and

comparing the light emission data from the [cell] lysate in the presence of the agent to the light emission data from the [cell] lysate in the absence of the agent, wherein a difference in light emission data is indicative of an effect on cell proliferation.

18. (Three times amended) An *in vitro* method for determining cell proliferation of a cell or population of cells comprising:

lysing cells containing a *Renilla* luciferase polypeptide or a polynucleotide encoding a *Renilla* luciferase; and

obtaining light emission data from the lysate *in vitro* [a cell containing a *Renilla* luciferase polypeptide or a polynucleotide encoding a *Renilla* luciferase] over a period of time wherein a change in light emission data is indicative of a change in cell proliferation.

31. (Twice amended) An *in vitro* method for determining the effect of an agent on cell proliferation, the method comprising:

transfecting a cell obtained from a sample with a vector containing a polynucleotide sequence encoding a *Renilla* luciferase;

[contacting the transfected cell with an agent suspected of modulating cell proliferation under conditions that allow the agent and the cell to interact; and]

lysing the transfected cells that have been contacted with an agent suspected of modulating cell proliferation to form a lysate; and

comparing the light emission data from the [cell] lysate in the presence of the agent to the light emission data from the [cell] lysate in the absence of the agent, wherein a difference in light emission data is indicative of an effect on cell proliferation.

63. (Three times amended) An *in vitro* method of screening mammalian cells containing a *Renilla* luciferase polypeptide or a polynucleotide encoding a *Renilla* luciferase to determine their susceptibility to treatment with an agent, comprising:

[contacting cells containing a *Renilla* luciferase polypeptide or a polynucleotide encoding a *Renilla* luciferase with an agent; and]

lysing the cells that have been contacted with an agent suspected of modulating cell proliferation to form a lysate; and

measuring light emissions from the cells in the presence and absence of the agent, wherein a difference in light emissions is indicative of the cells' susceptibility to treatment with the agent.